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FDA/DIA SCIENTIFIC WORKSHOP ON FOLLOW-ON PROTEIN PHARMACEUTICALS

BREAKOUT SESSION C

PHARMACOLOGY-TOXICOLOGY STUDIES

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Marriott Crystal Gateway
1700 Jefferson Davis Highway
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PARTICIPANTS

MODERATORS:

ANDREA WEIR, FDA/CDER

MERCEDES SERABIAN, FDA/CBER

JOY CAVAGNARO, Access BIO

JAMES GREEN, Biogen Idec

P R O C E E D I N G S

DR. EL-HAGE: We are ready to get started, if people want to come in and get seated. I am Jeri El-Hage. I am a pharmacology supervisor in metabolic endocrine drugs in CDER.

Our panelists today will be Andrea Weir, who is in CDER, in therapeutic proteins; Mercedes Serabian, who is in CBER; Joy Cavagnaro, of Access BIO; and, Jim Green, of Biogen Idec, our industry representatives.

Since we didn't have a plenary session this morning, we are going to conduct our session a little bit differently. Jim Green is going to give us a few intro slides to discuss the topic of--briefly discuss the topic of safety testing of biologics, in general, and then each of our other moderators will give a slide with a case study, discussing molecules from low complexity up to high complexity, and then we would like to have a discussion around each of those types of molecules.

We have a few ground rules. I don't know if some of you read them. They were handed out

this morning. We basically would ask anyone from the audience who wants to contribute to come to the microphone, identify yourself and your affiliation, and we would ask that you limit your comments to two minutes, two to three minutes, and I will limit the duration of the speakers if that becomes an issue.

In addition, Keith Webber announced the docket number this morning and if you have any additional comments you would like to make, formal comment submissions, you can submit those to the docket. They have reopened the docket from the follow-on meetings that were held last year. That docket number is 2004N0355.

So if you would like to provide written comments on this topic, we would welcome those.

We are trying to reach some kind of consensus opinions and identify things that we can't reach consensus on. That's the goals of today's meeting. We will form some bullet points as a result of our discussion tomorrow for discussion at the readout sessions first thing

tomorrow morning.

With no further ado, I would introduce Jim Green.

DR. GREEN: Thank you, Jeri. Welcome, everybody.

This actually is the agenda that we're going to attempt to follow today. I am going to review, briefly, several considerations that are unique to protein products, just to try to set the ground rules for us, and then charge the question that essentially was charged to us, that was indicated in the meeting materials.

There are going to be several cases that are going to be presented by my colleagues up here and then there's going to be discussion of the cases and based upon the discussion that occurs today, we are going to try to summarize that and try to carve out a path forward.

So I think to try to set the ground rules, which many of you are certainly familiar with, if you've worked with protein products, and this is primarily differentiating the safety assessment of

proteins from small molecules, and that there are unique features that are presented or challenges that are presented for a safety assessment of biologics.

There are some limitations of animal models. There is the concept of use of a relevant specie, which is a whole didactic series of lectures unto itself. There are issues of unique species specificity. There are issues relate to work that is performed essentially in animal models of disease, that work that can be used to support, in part, safety assessment conclusions.

There is the issue of immunogenicity, which you will hear about tomorrow, but immunogenicity, essentially, is also a unique issue for the safety assessment of these molecules, because it is a potential complicating factor which has to be considered during the design and evaluation of safety, as it can be determined in animal models.

However, it also is an opportunity to create or to evaluate relative comparisons of

different forms of molecules, from the perspective of immunogenicity profile, and, again, we are going to hear about that more.

There are unique requirements, as we heard about this morning, for PK-PD assessments. If you think about it, essentially, one of the basic tenets of toxicology is the concept of dose. Dose, in many folks' opinion, is equated to exposure, exposure is related to kinetics, kinetics is related to disposition profile, so they go hand in hand.

Having said that, there are unique issues that have to be considered for biologic dosimetry which are different from small molecules, and these have to be considered.

Then there's issues of non-traditional dose response and, in some cases, the infamous bell-shaped curve.

Now, what kinds of studies are currently used to establish bio similarity? Here are five points which begin with biochemical characterization to confirm structural identity,

biological activity to confirm potency and maintenance of mechanism of action, pharmacokinetic and pharmacodynamic assessments, which confirm dosing regiment.

As I had indicated earlier, the focus of our panel discussion today is going to be on the toxicology evaluation. When you think of toxicologic assessments, you think of therapeutic index and overall safety profile, as determined in a non-clinical setting. And then the clinical assessment, which is meant to confirm kinetics, safety and possibly efficacy.

So it's on the basis of this entire program assessment that the conclusion of bio similarity is supported or refuted.

Now, with respect to protein products and when we talk about essential data requirements and the concept of minimum data requirements, which many in the audience are interested in, probably the only thing that isn't up for discussion and debate, although this is probably even debated by some, to an extent, is the fact that you have to

have a complete CMC profile. You have to meet relevant state-of-the-art standards that innovators meet today and will meet tomorrow.

Those have to be met by follow-on manufacturers and the relevant ICH guidance is applied.

Now, additional data sets, and this is where the discussions occur, additional data sets based upon level of certainty from characterization studies, employing elements of previously mentioned technical assessment program, complement that data set and support or refute the basis for similarity and the conclusions derived from that.

As I indicated, the panel focus for this afternoon is on preclinical safety assessment.

Now, there are several issues that have to be considered when you're designing toxicologic studies. These are indicated here. They range from the availability of a relevant animal model to considerations related to types of toxicity end points, whether you're considering about a general assessment or a specific toxicity, which is unique

to the particular product that is being studied.

There are issues related to dose, dose multiple, and route of administration, and those are important considerations for supporting or refuting, again, an assessment of similarity or comparability.

Considerations in the design, also, one important one is whether you're dealing with a therapeutic index which is considered to be large or small and what concerns, essentially, that therapeutic index may present.

We are focusing on the active ingredient. We recognize that, right from first principles, the process that is used to make the follow-on biologics is different, different cell line, different reagents, different configurations, et cetera. Despite the availability of standard platforms, it's a different process.

So the focus of this assessment here is on is the active ingredient essentially behaving in the same way. The whole issue of assessment of product-related impurities is a different issue.

Is there an active control, essentially, which could be incorporated into the design of toxicologic studies to allow a head-to-head

assessment between an innovator and a brand product and the follow-on product?

Obviously, head-to-head assessments, from a scientific perspective, are ideal. That's the strongest data set.

Then there is the issue that was charged essentially for all of us to consider in our various panel discussions, the issue of complexity of the protein, low, moderate, to very high, and we are going to spend a little bit of time talking about what that might mean and I think it will be something we will be thinking about when we talk about minimum data sets.

So the question to the panel: In which situation would animal studies be needed and why? At this point, I'm going to turn the presentation over to Joy Cavagnaro to talk about protein complexities and lead us into the cases.

Joy?

DR. CAVAGNARO: Thank you, Jim. So I think it is important for us to state that this was a single question for the entire session and that when we say animal studies, we don't generally separate them out into PK/PD, toxicity, local tolerance, even though those are specified end

points.

It has been the hallmark of developing innovator products to basically, to use the government term, have a "two-for" to actually evaluate as much as we can in that animal model, when we can.

So it is important to understand, we have heard case-by-case and you will hear it throughout our presentation, and that is that-- what is the product, so what is case-by-case; what is the product, what is the indication, but what is the question.

So you'll hear some of our remarks in the context of what actual question that we might be asking.

So why do we do what we do? In terms of

the preclinical safety studies, the reason why we do these is to communicate risk, and that is risk to the patients. We heard at the opening lecture about the patient, and that is really why we are here, for the patient.

So we want to identify a safe starting dose and a dose escalation scheme, but now we want to understand comparability of the product now, so that we can assure, when we write that informed consent, which is what communicates risk during clinical trial, that the patient actually understands what they are getting and then, ultimately, in the label, which is the other opportunity for us, as preclinical scientists, to communicate risk in the product label.

So what we will do is--again, these were presented earlier. This is a little bit more detailed. I think they are in your notebooks--that we will posit our case scenarios in the context of three types of protein in terms of complexity. This would be the hypothetical single chain antibody, where we have molecular weight, 30,000.

This would be a non-glycosylated protein. It's limited in heterogeneity. It's an E. coli host and it blocks the soluble hormone.

It is a well understood mechanism of action and there's a lot of pharmaceutical knowledge on the protein and the pathway. The excipients are the same and the route of administration is the same.

Now, we can also get into delivery devices, but that's just a step above, but right now, this is what we will define as a simple molecule and moderate to high would be a receptor ligand, where there are multiple innovators, there is glycosylation, and, in fact, cyolation impacts PK. This would be moderate heterogeneity.

An example would be a CHO derived protein. The receptor is well understood. There is a defined organ toxicity. It is non-redundant cell protein and the sub-Q route, and it is formulated with a detergent. So you have to keep these all in your head as we go through the examples.

Then the last one would be a very highly

complex molecule, where it has multiple active sites, large molecular weight. There are multiple innovators. It is glycosylated, high level of heterogeneity, et cetera, CHO host, and the mechanism of action is only partly understood.

So, again, these are what we will try to address as we go forward, whether or not, in fact, any of these make a difference in terms of the expectations for the preclinical evaluation, and I think that's it. So we will go from there.

Mercedes will be doing the first case study, and then Andrea, and then I will do the last case study.

MS. SERABIAN: I just thought it was kind of interesting. I'm with the Center for Biologics and I'm in the Office of Cellular Tissue and Gene Therapy. So we regulate gene therapy and cell therapy products, and I got the easiest slide, I guess. So I thought that was kind of interesting.

For case one, and, again, similar to what Joyce said, you can keep in your mind, if you want, in terms of the protein complexity of the

monoclonal that she mentioned, but I think you can refer to recombinant proteins, whatever.

But the point is, basically, we're studying this scene that, at least in this case, the biochemical characterization, the innovator is the same as the follow-on, activity same as the follow-on.

We have in italics "nonclinical PK," because if we assume that the PK is performed in animals and then that's the same, also, as the innovator, then where do you go from there. Is tox evaluation required; if so, what types of studies would be required in this case?

Also, I may want to potentially propose if--one and two, I call it, the biochemical and biological activity are performed and are found to be the same as the innovator for the follow-on product, do you go on and do nonclinical?

So it's almost two things, in a way. In one case, we're assuming that the PK is done. In the other case, we are assuming that we stop at one and two.

So I don't know if anyone wants to take an initial stab at what they think should be done, assuming--let's assume that PK has been performed

in a relevant animal species and, basically, the innovator, the data are similar or identical, if you will, to the follow-on, in terms of tox studies, preclinical studies.

Do I have any takers in the audience who think yea or nay, and, if so, what; if not, what?

DR. EL-HAGE: I'd just like to make one comment. Basically, the legal and regulatory decisions about what will be required have not been made at this time. The purpose of this workshop is to seek input from regulated industry and what they think is appropriate and their justifications for the same.

This is your opportunity to give us your feedback.

MS. SERABIAN: Personally, I have my own thoughts, based on my experience. I was in OTRR since 1993 and when the reorganization occurred, I stayed in CBER and cell and gene therapy. So I do

have fairly extensive experience with these materials, but we want to hear your thoughts on this.

You can identify yourself.

DR. FACKLER: Paul Fackler, with TEVA Pharmaceuticals. To be honest, rather than make a comment, I was going to ask a question.

What would an innovator do, for instance, if they moved the site of manufacture and ended up with the same biochemical characterization, the same biological activity?

Ordinarily, would they do any toxicology evaluation under those circumstances?

MS. SERABIAN: If they simply changed the site, the physical site, you're saying?

DR. FACKLER: Yes.

MS. SERABIAN: Versus--you mean literally a new plant, new manufacturing plant.

DR. FACKLER: As an example, or, for instance, if they changed the cell line. Just to try to give us some basis for comparison for what the follow-on manufacturer might face.

MS. SERABIAN: Again, I think we're on the--at least in this case, we're basing the assumption on that the physicochemical

characterization is the same. If you change the cell line, in my mind, that's a major change and potentially could require additional preclinical bridging studies.

But I think, in this case, we're making certain assumptions and the assumption is that the physicochemical characteristics are the same as with the innovator product.

DR. FACKLER: I guess I would propose then that the follow-on manufacturer wouldn't do more characterization or more toxicology evaluation than an innovator would do under the same kinds of changes.

Again, I don't know what innovators do under those kind of changes. So really the nature of my question is what kind of tox programs are ordinarily done to show comparability after changes in process or changes in manufacturing site and so forth?

MS. SERABIAN: I think, and, again, I speak from my own experience, in general, usually, animal PK studies have been done and some type of a small bridging study has been performed. Again, it depends on the product. It depends on the potential toxicities that were seen before as to

what the focus of those preclinical studies should be.

DR. COSENZA: Mary Ellen Cosenza, from Amgen, as an innovator. I'll try to answer a couple of the different questions, as a couple different scenarios came up.

If we change the cell line, we most certainly would do quite an extensive preclinical package, including PK, at least probably one month of toxicology in the most relevant animal species, potentially some irritation studies, IB tolerance studies, depending on the route, if there are multiple routes being used.

If we change the site, we might not do quite as extensive, but when we have looked at change in manufacturing sites, we have done up to a

one month package, so a similar type of package.

If we just looked at scale-up, going from one size reactor to another, we would most likely not do quite as an extensive package, but we would certainly do some animal work. So we would at least do PK, to start with, in animals to make sure that there's not additional changes there.

I guess my question on here, this biological activity, saying the innovator equals the FOPT. If that is in vitro, then we would probably do more extensive preclinical work, because if that is in vitro, you can find some very big differences in vivo.

Certainly, I can give you examples where we have made changes, glycosylation changes in molecules, that the in vitro potency difference goes one way and then when you go in animals, because of the differences in PK, the actual potency in vivo is exactly opposite what the potency is in vitro.

So I would be very wary of depending just on in vitro potency.

MS. SERABIAN: So would you use potentially normal animals, disease model, or it just depends on what you get?

DR. COSENZA: Well, some of that will depend on what the molecule is and how you characterize it to begin with.

Most things, I think people now are finding that normal animals give you the best historical data to compare to than disease models, but, of course, there are some molecules that don't have any activity in normal animals, and so you might need to use a disease model there.

MS. SERABIAN: So you're saying, in any case, some type of preclinical studies would be done. The extent of those studies depends on the extent of the changes that occur.

DR. COSENZA: That's right. I think I can agree with that.

MS. SERABIAN: Thanks, Mary.

DR. CAVAGNARO: I don't know if this is legal, but people who know me know that I don't do things very legally.

So we had, on a slide, preferred, the innovator, the reference compound, and the test compound, whatever, the follow-on. The reference compound was preferred.

That is something that I think is worth discussing. The EMEA documentation suggests a

reference compound with all these types of preclinical, and we heard this morning that reference compounds, maybe we would need multiple, if it was multisource, multiple compounds to compare it.

I guess I would like to hear a commentary on the absolute requirement of having a reference compound during the course of whatever studies we discuss.

DR. ANDREWS: Well, I'm not going to comment on that right now. Paul Andrews, ImClone Systems. My answer is no, for the reason that I don't believe you can design a tox study in primates with low numbers of animals per dose group, the inherent biological variability between monkeys, that will detect a difference in a

toxicity end point for the situation we're talking about, where the biological, physical characterization is identical. The PK is identical.

I wonder if there is any case where you have a product under that circumstance where you then went on and detected a difference in a toxicity end point, many of which are fuzzy and qualitative.

MS. SERABIAN: Okay. Paul, you're saying--and, again, we have here therapeutic index. If the therapeutic index is fairly narrow and with the innovator product, there are toxicities, bone marrow toxicity, whatever, toxicities that have been seen, you would--

DR. ANDREWS: Let's just say you would think if there was a 20 percent difference in potency between the innovator and the follow-on product for that end point, bone marrow toxicity, do you really believe you would be able to accurately pinpoint that difference in a primate study?

MS. SERABIAN: If you did the first time, why wouldn't you the second time? With the innovator product, you're saying a 20 percent

difference between the--

DR. ANDREWS: You'd see it. But would you be able to say there was a difference between the innovator and the follow-on in the toxicity to the bone marrow?

DR. GREEN: Perhaps I can help on that. I'm not aware of perhaps an example of an innovator and a follow-on, but within an innovator company, essentially, when a cell line change or process changes have been made, that kind of potency difference was detected essentially in the non-human primate assessment.

I think one thing that I would preface that remark with, what I think we're trying to get at with these case studies, and recognizing that years of work, essentially, is usually done, essentially, in preparing a registration dossier, and some have essentially stated fairly categorically that there would be a requirement or

there would absolutely be no requirement.

I think one of the issues with that kind of statement is that what we're trying to get at with the concept of minimum data sets is what would be a reasonable expectation for kinds of data that you would have in your registration dossier to allow an approvable decision.

I think general realities, the problem with general realities, essentially, is that you can always find exceptions. So if we're talking about, essentially, toxicologic assessment, what this case posits, essentially, is in those situations where your available analytical techniques and your available bioassay techniques, whether they be laboratory or animal-based, are scoring the conclusion of no differences.

Under those circumstances, would you progress, essentially, the hierarchy of assessment to include a kinetic assessment, to include a toxicologic assessment, and would that essentially also derive what might be ultimately a consideration for what might be necessary for a

clinical assessment in that case?

So one position might be that, in any case, you would be expected to, from a perspective of a registration dossier, which many have defined as a full complement of data. Now, the problem with that term, essentially, is full complement means different things to different people.

Is it the innovator types of studies? Is it the innovator studies exactly or is it a series of studies which address those particular end points based upon the knowledge which has gone before it?

So I think that is what we are trying to get a dialogue on, because the specificities around specific cases like this, I think, are what will hopefully influence the agency's decision on ultimately what might be requirements in a situation like this.

MS. SERABIAN: There's always justification. There's always exceptions, if you will. But, yes, I think it's either--you know, I'm not giving a yea or nay, but based on what is in

front of you here, there will be--I mean, there's a couple other cases where it may have some of what you're thinking.

DR. GREEN: This case, I question whether a tox study would have the power to pull out a difference based on this case.

DR. CAVAGNARO: We're not only talking about non-human primates, too. These are short-term studies and looking at relative immunogenicity or relative difference in kinetics. So it's not that we're going to be limited to just looking at non-human primates, as well.

DR. SOLTYS: I'm Randy Soltys, from Genentech. The one thing that I think you need to pay attention to is the fact that even with small, what would be seemingly minor changes in molecules, it may very well be a change in the immunogenicity profile, there may be an off-target hit that can very well be picked up by those primate studies. So I think there is a differentiation.

It's one thing to understand the comparative dose response relationships between the

innovator and the follow-on molecule, but there may be other things beyond that that you need to have an understanding around and the only way to do that is in an animal study.

Ultimately, you want to do it in the clinic, but to get to the clinic, you need to do something before. It's not to say that a preclinical model is going to be predictive every time. In fact, most often, it's not going to be, and you won't derive any comfort from that, but when you do get a signal, it will give you that much more sensitivity towards the particular issue.

DR. GREEN: So can I maybe ask you one question on your comment? Your comment regarding predictivity, is that related to immunogenicity or related to safety overall?

DR. SOLTYS: Predictivity for immunogenicity more than anything else.

MS. SERABIAN: I think one issue, too, is not just the performance of toxicology and safety studies, but how extensive they should be. People use the term "full complement of studies."

Are we talking carcino--I mean, how far do you go with the performance of these studies? Given the case that you've got here, the example,

any comments with respect to that, as to do we just perform a small--again, depending on the dosing regimen, repeat dose study, let's assume that's what it is, a two or four week study and we collect safety pharmacology and PK/PD parameters in that one study, just sort of a one-size-fits-all type of study, or do we do a multitude of different studies?

MS. MIKER: I'm Christine Miker, with Barr Laboratories. I guess looking at the low complexity case, I'm assuming that full characterization has been done and I know exactly what this product looks like.

In that case, if we're concerned about aggregates and impurities and things of that sort, I think that's a different question for immunogenicity. But if I can determine that the aggregates are the same and everything is identical, then I would propose that there is no

animal study at this point and we deal with the immunogenicity from a different standpoint.

At least I haven't been concentrating on the immunogenicity for this session. But if I know that this is the same exact compound and I've got everything the same, then I would say no animal studies are required.

MS. SERABIAN: For the simple one like this. Same compounds within the limits of the assays that you are given.

MS. MIKER: And assuming that I've done a human--I can go into human PK, that we're talking about the same dosage form, same formulation. So you're not going to have any of those questions. I would propose that there aren't animal studies required at this point, and then when we get into the higher complexity, then you get into some different questions.

MS. SERABIAN: What about, I'm just curious, therapeutic index, if there was a distinct difference in your particular material, for example? There's a very narrow range, the TI is

very low.

MS. MIKER: That's kind of a case-by-case basis. I'd have to look at it on a product-by-product basis. I wouldn't want to just make a general statement that we wouldn't do it, depending on what the therapeutic index is, but if it's a very wide therapeutic index, I think you have more leeway versus a very narrow therapeutic index.

So I would hate to say that, just a blanket statement.

DR. GREEN: Could I ask one question, before you leave? The issue essentially in that particular situation, where you have described basically the formulation components being the same and I guess we have a very good understanding of the product attributes and the product attributes have been confirmed, essentially, by the analytical and characterization studies that have been done.

How does that address the issues related to process impurities that might, in a sense, induce a reactogenic reaction? How do you assess

that?

Is there a way that you can get that information, essentially, without any animal study?

MS. MIKER: It depends on what we found in the chemical characterization. Are you assuming that they haven't been detected?

DR. GREEN: I think just the issue--we deliberately focused our discussion here on the product itself, but as we heard this morning, and I was actually somewhat surprised at how unknown actually many of the process and purity profiles are and that whole degree of heterogeneity which is conferred by those new processes.

I think there's sufficient level of concern, even with a profile like this, some minimal assessment in an animal model, and perhaps it can be essentially assessed within a dosimetry study, where you are confirming kinetics, but paying attention essentially to that aspect would also be able to be done as opposed to stumbling on that initially in your first human trials.

MS. MIKER: I wouldn't disagree

necessarily at all. I mean, it depends--I can see your point.

DR. COHEN: Hellel Cohen, Novartis. Thank you, Jim, for making the point I was about to make, essentially. Three points.

First of all, by definition, we have case one, case two, case three, increasing complexity. The reality is, by definition, we've all agreed, when you from innovator to follow-on, by definition, you're going to use a different process; albeit, you may model it, but it's still going to be a different process, different facility, different cell line.

By definition, all of these are major changes. So it's not a question about the complexity of the protein that you're trying to copy. The change that you're making is a complex change and requires full analysis. So we really can't get away from that.

In terms of streamlining what needs--now, that gets to the point that Jim just made, which is the protein itself, the fact that biochemical,

biological activity might be the same, but their incipient, adventitious agents, impurity profile will, be definition, be different, and toxicology studies are the means by which we detect these signals.

So you really can't dispense with those completely.

In terms of what you might be able to streamline, I think it's fair to say that if some twas uncovered with an innovator, it might not be necessary to repeat that exact same study. By the same token, if an innovator has done an exhaustive set of studies on a particular question that may have arisen and found that this particular item is not of concern, that might be an item that can be eliminated.

So there are opportunities to streamline, but it really has to be based on what is known about the given products.

Finally, about the idea of just going directly into human studies, based on what is known of biochemical and biological activities, it was

proposed this morning, I know I would feel very, very uncomfortable putting human beings at risk without a modicum of safety check in an animal system.

Now, it need not be nothing more than a gross check of toxicology. It has to be carefully done, but, really, you can't put people at risk without doing some level of checking in an animal system.

MS. SERABIAN: So then we get back to the consent form, at least one thing, an issue.

DR. COHEN: I would not want to put a consent form in front of a patient saying this product has never been studied before in any animal model, would you like to be the guinea pig.

DR. CAVAGNARO: Well, that's a little bit strong, but that's the idea. Can I just comment in terms of impurities?

I think it is important to understand, because one of the first questions asked is is it different than, are you requiring something different than an innovator, and we do not test for

impurities, by definition, in terms of designing our preclinical tox programs for the innovator.

So we do risk assessments. It was stated this morning that the adventitious agents were off the table, but if there's a chemical of concern, it's almost dealt with in a CMC.

We do a risk assessment of that chemical. We recommend removing it. But in general, for innovator compounds, we don't design toxicology studies for impurities.

We look at the relevant animal model. So we have argued against just doing non-relevant models just for the sake of looking at impurity testing.

So the level of sensitivity is not there. It's not true that we do that. We don't do genotoxicity studies for impurities in the process.

DR. COHEN: You are absolutely right. There's two questions here. One is that if you are designing something you know that is related to the product, per se, and the other one is a gross check of the unknowns.

Now, I posit that you really do--the tox studies that we do are, to a degree, a gross check of the unknowns, necropsy of all major organs.

It's that which I am referring to.

If you have, at some point during the process development, an impurity and you want to isolate and test the toxicological profile of that particular impurity to find out whether it's clinically relevant, that is a completely different line of investigation. It may or may not be necessary.

I agree with that completely. In fact, a follow-on may detect an impurity. You may follow through, purify, isolate, characterize that, do a tox study, and find that it's not relevant, in which case I would say that even though the impurity profile might be then different than the innovator, it may not be relevant.

But still you have to--I would feel more comfortable with some degree of a general toxicological safety study, if nothing more than to make sure that the different process yields a

product that doesn't have any surprises. That's really where I'm coming from.

DR. CAVAGNARO: So it's process related, not product related. It's not variants that you're talking about.

DR. COHEN: That's my point. Picking up what you had just mentioned, if you do find a product related impurity, that is a completely different line of thinking, and you can pursue that, if you choose. That's a different line of thinking.

MS. SERABIAN: So it sounds like what I'm hearing, in general, is even though this is equal to this, this is equal to that in a slide, that assumption can't necessarily be made in terms of the follow-on product.

So some type of preclinical information needs to be generated. The extent of what that information is, I guess, depends on the product of interest that you're looking at, as well as the therapeutic index as to what to focus to.

For example, if there were some

reproductive toxicology issues before, then, obviously, that's going to, I would think, be a focus for this material, too.

I'm not sure time-wise where we are.

Head-to-head comparison. Just thoughts on that, in a study with the innovator to the product in a toxicology study, PK, tox, et cetera.

DR. REYNOLDS: I'll speak to that. Theresa Reynolds, Genentech. I don't know how you would know what the innovator's data were. I don't know how you would know what to look for without doing head-to-head work.

The studies that are submitted have certainly been submitted by the innovator, but they're not available when you pull an SBA on something. All you have is the interpretive information, but you don't have the line listings.

So for you to really do a head-to-head or to really know what you're looking for and to know whether you fully compare, I think you have to do a head-to-head comparison.

MS. SERABIAN: Any other questions,

comments?

DR. FACKLER: Paul Fackler, with TEVA. I understand the concern about impurities and I guess I misunderstood when I read the assumptions were that the products were the same.

I presume that the product is the active ingredient and its impurities, if you will.

The same conditions exist in the small molecule business, where different processes are used to manufacture APIs, and using those different processes, different impurities exist.

Now, I know with small molecules, tox studies aren't done as part of an abbreviated approval process, and I guess, under case one, where we are talking about a very short protein, if you will, where it is fully characterized, and assuming that the impurities are equally well characterized, I'm not sure that there is value in doing toxicology.

I understand that you can't make a comparison to innovator, but I'm not sure, if there's no tox issues associated with it, what

value that comparison would have.

DR. GREEN: I think if you just focus the discussion on reactagenicity locally, that's a good starting point.

I think your small molecule contrast, that's an important one, but the history there, essentially, with small molecule development, as you know, is that there are generally accepted guidelines with respect to when these impurities, I think the strike level is .1 percent, need to get qualified.

Certainly, if a synthesis presented a new impurity that exceeded that level, I would think you would be in a position of perhaps having to qualify that, depending upon the nature of that impurity.

But you always have to have the option of changing the synthesis and purification to eliminate that purity below certain strike levels.

So I think that's a fact for small molecule synthesis that many of the biologics I don't think can meet that test.

I think, also, the impurity levels for the processes, these impurities still are very much undefined. So I don't think they're defined with

the kind of precision that you have for small molecule impurities.

DR. CAVAGNARO: I just want people to, again, think about the combination of studies, when we talk here, in terms of PK versus tox. I don't know what the expectation--what people, when they say tox, what they mean.

But I think it would be a missed opportunity, we feel, designing these animal studies not to look at some tox end points when you're doing an animal study. So you do PK. We would always look at local tolerance, I mean, to do a separate study.

So if you're going to evaluate an animal species and make it as useful as possible, I think it would be--I mean, I think in terms of designing studies, maybe that is perhaps an understanding that folks have in terms of what is a tox study; is it this expectation that it's this huge,

time-consuming, very expensive, using lots of--I don't know the expectation.

But I think for those of us who do animals, we try to get as much information as we can out of that animal, and that is what we have done in terms of our toxicology studies for the innovator.

We ask multiple questions whenever we can in terms of the study.

MS. SERABIAN: I think the key is are animal data needed, and, if so, to what extent. You're right. Especially if it's a large animal model, you can collect safety end points and we ask for that all the time.

They are very resource-intensive studies and to just do a study simply collecting blood for PK and not anything else, I just find amazing, I think, sometimes.

Any others? Then we'll switch to the next one.

DR. GREEN: Did we get to the level of complexity issue, within this simple example? It

didn't make any difference. Okay. I'm sorry. I missed that.

DR. EL-HAGE: Can I ask, for those of you who made comments, if you have business cards with you, if you could provide them to our transcriber at the end of the session, it would be greatly appreciated.

DR. WEIR: Moving on to case two here. We have a slightly different type of product. In this case, the biochemical characterization, I think, which was dealt with quite nicely in some of the presentations this morning show that the innovator was not the same as the follow-on product.

This, of course, was something like changes in glycosylation.

However, in this case, the biological activity was shown to be similar between the two products. Certainly, the assays that are used for measuring biological activity tend to have more variation than some of the biochemical characterizations.

This case, again, we have made the

assumption that there is a nonclinical PK comparison has been conducted. If someone doesn't think that is necessary, certainly, feel free to contribute that comment.

In the case of the nonclinical PK comparison, it was shown that the innovator was equivalent to the following product.

So, again, the question is should any type of toxicology be done for this product, for this follow-on product, and would the extent vary with high versus narrow therapeutic index and, also, what impact, if any, would the complexity of the molecule have on the type of tox studies that would be needed, referring to that Joy gave earlier regarding complexity.

Any first-comers on this?

DR. HEIDEL: Shawn Heidel, Eli Lilly and Company. I look at this case and the first thing that jumps out at me is immunogenicity.

So if you don't have the same biochemical characterization, how do you know whether it's going to have an increased immunogenicity response?

This is pretty critical, given some of the recent cases we have had.

So in addition to what everybody has been saying about toxicology in the first case study, I think you also are going to have to do some kind of immunogenicity assessment, immunotoxicity assessment, and the length of that has to be as long as it takes to get your answer.

Usually, you're looking at at least a one month study, I would say, and in that study, I think that you need to probably also do some kind of immuno tox assessment over and above your immunogenicity.

DR. WEIR: So you're proposing doing immunogenicity studies in animals, like a comparative immunogenicity.

DR. HEIDEL: Correct, with the innovator and the follow-on, because if you don't have that comparison, you're not going to be able to tell what the answer means if you just use the follow-on. So you always have to use the innovator product.

DR. WEIR: I guess the next question that begs asking, that's sort of outside the realm of this discussion, is doing immunogenicity in

animals, can that be extrapolated to humans, but I think that is probably best left for a different session.

DR. HEIDEL: I'm not going to touch that one right now, I'll tell you that. But my opinion is yes. As long as you do a comparison, you're going to get an answer out of that study that I think is meaningful.

DR. WEIR: Any other opinions on this?

DR. ANDOLINA: Vincent Andolina, TEVA Pharmaceuticals USA. I have more of a question.

We haven't defined how the follow-on product differs from the innovator. It would be a common sense approach to require the follow-on product to support how it differed from the innovator. Did you find some impurities in the follow-on that weren't in the innovator? Is it just--obviously, if it's not the same active, it can't rely on the innovator's safety and efficacy

data. Obviously statement.

DR. WEIR: For these case examples, we really didn't have any specific differences in mind as far as innovator versus follow-on, but it's a good point. It all depends on what the nature of the difference is; how do they not compare, how do they not compare with regard to the biochemical characterization, and could they be so far apart that the whole innovator pathway might not be the way to go.

DR. ANDOLINA: Right. I think that's a good point and I think actually what that first bullet was attempting to capture would be would that be, in fact, a surprising result that you would be confronted with, given the fact that you are beginning with a new cell line, you have new process configurations, essentially, reagents, et cetera.

So when you characterize that analytically, the fact that you see differences, are you surprised? We do this from an innovator perspective all the time and we see differences,

but it depends upon essentially what is known about the product attributes and what kind of perspective you can put on those changes.

So what this case also illustrates is the fact that does the biological activity or kinetic assessments or even toxicologic assessments override, at that point in time, what might be concerns that are pointed out in an analytical consideration, and that's something to think about.

Now, certainly, if the analytical characterization showed that the product attributes were different and we understood those product attributes sufficiently from a structure reactivity perspective, then you might expect that the dosimetry may be different.

If the dosimetry is different and the product attributes are different, then I think you have a different molecule. If you have a different molecule, once you have reached that conclusion on the basis of that hierarchical assessment, then I think the bar is very high with respect to what

would be looked for from a registration perspective.

So that's something to think about from this example.

DR. NAVEH: David Naveh, Bayer. I have a question to you or other immunologists in the audience.

Do you think that if you had a follow-on and you did a head-to-head by buying a vial of the original molecule and you put that in an animal and you would develop or get the antibodies developed quicker or faster or to higher amplitude in an animal model with the innovator, it would be it's more immunogenic and vice versa.

Does that have any meaning at all in the context of man? I'm talking about the use of animals as predictors for immunogenicity. That is what I think you were talking about.

I had three questions, but that was the first one.

DR. HEIDEL: Clearly, there isn't really much data out there for that. We were talking

about this last week, as a matter of fact.

In my opinion, if you have increased immunogenicity of a product that could cross-react with an endogenous human molecule, then I'd be pretty darned concerned about that.

In other words, if you have a follow-on that's--I'm going to pull out the EPO example, which everybody likes to talk about.

So if you run an animal tox study and you have a new EPO molecule and you have increased immunogenicity in your animal model over what the innovator had, I would be pretty concerned about that.

DR. NAVEH: Of course, I'm just asking about the relevance of animal models. This is the big concern. I'm not disputing the concern. This is indeed the heart of the matter.

I'm asking how would you interpret animal data, if you put the human protein in rabbits, rats, primates, and you take the vial of the originator and the follow-on, and let's assume that you get, after 15 exposure days, with the

follow-on, antibody development, and after 25 days with the originator.

How would you interpret that data?

DR. EL-HAGE: Excuse me. Could I interrupt you? I think this is a discussion for one of tomorrow's sessions. We're not trying to talk about predictivity of animal immunogenicity data to clinical immunogenicity data.

We're trying to say could you do a head-to-head of the comparator to your new product as a screen for marked differences. How that the predicts to clinical we will discuss tomorrow, and I really don't want to spend a lot of time on this issue in this discussion.

DR. CAVAGNARO: I agree, but let me just--so I think that we use it in terms of relative immunogenicity. I mean, what we say is humans don't even predict humans.

The incidence of immunogenicity is rare. Oftentimes, it's not always dose-related, et cetera. So I think we use our animal models, but it's important here, because the point was brought

up that there could be concern based upon biochemical characterization, that you may increase immunogenicity.

So we look at relative immunogenicity and that's as best as we can do. Depending on in terms of the level, I know Lilly screens to select for insulin analogs to be less immunogenic.

The problem is that the validation of immunogenicity is always in human, and we have incredibly immunogenic molecules in animals.

We don't put them in humans without premedicating humans, giving them steroids, et cetera.

So even to look at predictive value of an immunogenic, a human protein that is obviously going to be immunogenic in animals is hard, because we don't even allow the patient to actually answer the question for those molecules that are incredibly immunogenic.

What we do know is that molecules that are incredibly immunogenic in animals tend to be immunogenic in humans, but that's as much as we can

do with our animals.

DR. FACKLER: Paul Fackler, with TEVA. With regard to comparative toxicology studies, I'm not certain they have value unless the follow-on protein is looking to be interchangeable with the brand product.

There certainly might be cases where a follow-on product would want to gain access to the market without necessarily being interchangeable.

So I guess I have yet another question. When the brand process changes and you go through the comparability protocol to show that the changed product is similar to the original product or the comparator, whatever, our comparative tox studies don't under those circumstances, because I think that is an important analogy for what we're talking about to a follow-on product.

DR. GREEN: The answer to that question is it depends on the nature of the change or the aggregate numbers of changes that perhaps are being assessed at any point in time.

In that situation, the answer is yes. So

I think one of the issues that you--without confusing this issue with interchangeability, what you're talking about trying to get at from these toxicologic assessments is is the preclinical safety profile the same; is that conclusion the same.

That's why I like the analogy essentially presented by two of the presenters this morning, the elephant analogy. People tend to look, essentially, at their assessment from their own perspective.

What we are talking about here, I think, within the context of minimal data sets is an overall data set across a spectrum of disciplines that allows a conclusion of sameness or difference.

With respect to toxicology, it's sameness with respect to the predictivity of the safety profile as established in animals.

So depending on how that profile is established, on a head-to-head basis, where dosimetry can be matched, where the complications with immunogenicity can be excluded, if you can

conclude that this profile of a relevant animal specie is the same, that supports many things, the support of the clinical assessment that may be needed to support that therapeutic.

If it's different, then it's a different story.

DR. WEIR: I think especially if you're talking about a product that does not have a very wide therapeutic index, I think you would feel more comfortable if you had the innovator there for the head-to-head comparison.

That way, you could put more value on your toxicology study and perhaps allow for a more aggressive approach in the clinic when you start using the follow-on product.

DR. GREEN: Can I just make one comment about the immuno--I know we're not supposed to get into the immunogenicity profile, but I think it might be helpful to illustrate this one point.

Many of the protein therapeutics, yes, they are, in certain cases, highly immunogenic, but surprisingly, surprisingly, either just the way

that they are made, and I can think of many humanized antibody examples, for example, for instance, that in non-human primate species are remarkably non-immunogenic.

Now, in that particular situation, where you were testing an innovator product that had that kind of profile versus a follow-on product and you came to the conclusion that the follow-on product, for some reason, had, let's say, a 25 or 30 percent immunogenicity incidence rate and it was appropriately characterized, where the innovator product, in that same head-to-head system, was very low, I think you would be concerned, and legitimately so.

Now, that is the kid of assessment that I think would carry over, from my perspective, into the kind of clinical considerations with respect to what you need to know when and early and how much.

So I think that is an important point that I think you could pull out of these kinds of studies when they are properly done.

DR. FACKLER: I don't think there is any

question that these studies have value. The question, I think, is whether or not they are necessary to fully characterize the product.

As far as sameness, sameness isn't the only end point. If, for instance, the follow-on product were less toxic or had a better toxicity profile, it wouldn't be interchangeable, but still might have some value to the public.

We talk a lot about sameness, but I don't think, in the context of toxicity, sameness is necessarily a good thing.

DR. WEIR: And, certainly, you wouldn't want your follow-on product to be more toxic than the innovator, but I think having as thorough a toxicology assessment as possible, have that be done, does definitely characterize and is part of the full characterization of any product, whether it's innovator or follow-on.

DR. NAVEH: So, again, not being an immunologist, if you had a murine antibody as an innovator product and your animal model is a mouse and the follow-on would come with a humanized

antibody, you would get significantly more higher immune response with the follow-on.

I'm saying that it's not an a priori situation that animal models are relevant for predicting immunogenicity, as is immunogenicity of a tiny change in a product.

We're not talking about finding out whether a new molecule is inherently immunogenic, but whether a tiny modification is new antigenic, and I contend that, for that, animal models have limited value.

So I think that if you bring the impurity levels down to the standard levels which we are used to in the biotech industry, the only way of addressing this issue is in a clinical--and my premise is that if there would be such immunogenicity, it would be actually, in people, transient, but it would be broad. That means most people that would get the drug would actually elicit an antigenic response against it.

I think the only way to check it is in the clinic. And let me just finish one, and I will

just sit down.

The other kind of antigenicity is against impurities. I think that is more difficult, because there I could see a situation where you would say that you would only have it at a very low proportion of population, say three people out of a 100, and there, the power of the trial of the follow-on would have to be very significant to capture that.

But gross immunogenicity of a follow-on product I think needs to be checked in the clinical trial setting.

DR. GREEN: I think that is a point that I certainly am not debating, but I tend to look at immunogenicity, and I think many in this audience do, as just one other toxicity.

And I think, again, to understand the scope of the assessment that is done in these kinds of studies, this is one aspect that you have to understand very carefully in order to interpret whether or not you have a valid test system.

To that point, if you are investing that

kind of effort to try to confirm whether or not a therapeutic ratio between an innovator and a follow-on product is the same, if you see a difference in the signal that is conveyed on the basis of immunogenicity qualitatively, I'm saying that should be treated just as equivalent to any other signals that you may see in the biochemical characterization being different, the bioactivity being different, the dosimetry being different on the basis of kinetics, and you may conclude, on the basis of all of those assessments, that there are sufficient properties that are different in this molecule to warrant a very extensive clinical program.

You could conclude, on the basis of those same assessments, that the differences essentially are not significant. In that case, then a limited clinical development program may be appropriate.

That is within the context, I think, of what some of these examples are trying to highlight, those kinds of differences.

DR. WEIR: In the case of this type of

product, the innovator not being the same as the follow-on with regard to biochemical characterization, does anybody think the difference in therapeutic index of products or the complexity of the molecule would strongly influence or influence in any way the type of toxicology assessment that is done, or if the biochemical characterization is different, does that automatically state to anybody that tox studies, at least of some magnitude, should be done?

DR. OLESON: Frederick Oleson, from Cubist Pharmaceuticals. I had a comment on that, as well as the issue of whether or not you should be doing tox work, getting off the immunogenicity issue, because that can go on forever.

This is a case where you have biochemical differences of some sort and while the PK, probably because the sialic acids are similar, is similar or equal and the biological activity, the receptor binding may be equal, it does--the case was there was defined organ toxicity.

So I would be concerned that that

biochemical difference may not be related to receptor binding that is part of the efficacy activity, pharmacodynamic activity, but could be potentially related to toxicity, and that is really a powerful reason why you would really need follow-on tox studies of some sort one month or whatever length based on the innovator product.

And, certainly, in the case of a narrow therapeutic index, where that difference, the potential of that having a change in dose response, that's even more reason to make sure you do that.

DR. WEIR: Any other comments? If not, I think we will move on to case three. Joy?

DR. CAVAGNARO: So my case then is where the biochemical characterization is similar and the biological activity is similar.

It's a bit of a variation on the theme of case one. So if we went forward with a nonclinical PK and now we find that the PK is different, where do we go.

The clinical pharmacology section, I think, is arguing that this could very well happen

all the time, and so we'd have to deal with it, so why don't we just skip it and then just go right to the chase for the human study. So that's something to think about, to the point that if we are in non-human primates, it may be difficult to show 80-125, and it might be a little bit easier for rodents, because we have at least numbers anyway.

So if we're having to do something, if we decide that we do something or we're having to do something and it ends up in non-human primates, then it's a very real likelihood that we may get a difference here. So that would be something for consideration, as well.

DR. HEIDEL: In this case, I think that Mark Rogge had a wonderful example this morning in his slide set, which is that the efficacy of the molecule is based not only on its biological activity, but also on its PK.

So in this case, if you have a change in PK, then you could potentially change the activity in the animals and humans to a great extent.

And since, with biologics, toxicity is

usually an extension of pharmacology, I think it is very important to run a toxicology study for every case of this.

FROM THE AUDIENCE: I think one of the challenges on this one is what is the driver behind why the PK is different. So is it just an assay variability? Because sometimes these protein assays are variable within themselves, so they're not quite meeting the 80-125 percent rule.

But that could also mean a number of different things. Is the molecule actually being handled differently in the body, and so that's why the PK looks different.

If it's a real PK difference, which then leads to, as Shawn said, some of the issues that Mark Rogge talked about this morning, which means this could be getting to totally different places.

Now, in this example, in case three, when you go back to the high complexity thing, this is a molecule that has more than one receptor, has a receptor for--I think it said for glycoproteins, for glycoforms. So it really could be the whole

way the molecule is being handled. That would be a very big concern.

But if it's just an assay difference, which is why I think someone mentioned to you this is going to happen all the time, that's a very--that's not an uncommon thing to see and can be very puzzling.

On the other hand, sometimes these assays can actually tell you something about the activity of the molecule, because these are biological assays. If it's an ELISA or it's a second capture kind of antibody assay to find the molecule itself, it may mean that the confirmation of the molecule that you're not picking up in these top two lines are actually showing that there's some confirmational difference to this molecule, and that would be a very big concern.

So either way, I would do more toxicology work, for sure.

DR. CAVAGNARO: And you would go forward. I think, again, it was alluded to--

FROM THE AUDIENCE: Well, I don't know if

I would go forward. I guess it would depend on--I would want to do more work. I would want to figure out whether we think this is an assay difference, whether this is a binding difference, whether this is a true handling, distribution difference, before we went forward with the molecule at all.

DR. CAVAGNARO: Let's say this is phase three scale-up to the point of when we're discussing is it different than for an innovator.

Let's say that phase three trials were complete and now your to be marketed product has this change. That's the hard question, whether or not any of this means anything.

FROM THE AUDIENCE: Thanks, Joy. Well, that's not the same as the question on just the follow-on biologics.

If you're talking about a molecule that now you've been going--you're the innovator and you're going through phase one, phase two, and now you're into phase three and you've made some change in manufacturing.

DR. CAVAGNARO: I don't know. Is this a

fair question? If you saw this profile and it's your to be marketed and you've done your clinical trials, what is the recommendation to go forward? I mean, I think that that's--

FROM THE AUDIENCE: I guess I would ask why were you going back to begin with to do the PK study. So if you were doing that because you made a change in cell line or you made some other manufacturing change.

DR. CAVAGNARO: No. This is the to be marketed product now. This is what we're going to launch and we don't have any phase three. We're changing sites and now this is a launch material. We have shown biochemically it's the same, biologically it's the same, and somebody has done an animal study and messed it all up. I mean, that's real.

So what--and then do--

FROM THE AUDIENCE: Like I said, I think if you got this point, you had this result, you would want to do more investigative work, and it may well include additional animal work.

But if the driver for doing the PK study originally is because you made a manufacturing change, a site change, a cell line change, that

would go back to case one, where we would do additional toxicology work, comparing the original molecule and the second.

For example, we had a molecule, the original tox work, and the early clinical trial work was done by hybridomer produced molecule, and then we were able to change it to a CHO-based manufacturing process, and we did do additional PK and toxicology work on that molecule.

DR. CAVAGNARO: And you should have done.

FROM THE AUDIENCE: Yes. Well, I just want to make sure people know we really do that stuff.

DR. CAVAGNARO: Right. It's different. Right. Again, I think we do these animal studies really to facilitate our clinical, again, learn to--and that's why we do them, not just to do them.

So I think what you've heard, in terms of Jim's remarks, that learning some of the

information here can actually streamline your clinical program.

Is that the point you made?

DR. GREEN: One of them.

DR. CAVAGNARO: One of them. Do people think it makes a difference in terms of the complexity of the molecule, therapeutic index?

DR. NAVEH: Only in the sense that you are not sure whether your characterization is identical. But I think what's important are the potential toxicities. Nobody touched upon presentation, hypersensitivities, et cetera, et cetera, which could vary with formulation, particles and the like. We talked about immunogenicity.

So I think that the key is the safety profile of the protein and not necessarily its inherent complexity, except that you are never sure if it's more complex if it's identical.

DR. GREEN: I think that's a good point and maybe what I might add to it, and, again, this sort of gets back to I tend to lump anything

related to an immune response in these test systems in one bucket.

It's one thing you look at and you're concerned about, and hypersensitivity reactions, I mean, those are extremely difficult to predict in any way, shape or form from these kinds of studies, and even in the clinic there are issues.

But I think the issue really goes on what you know about the nature of the molecule. For example, a pleiotropic molecule versus something that has high specificity, and you understand unique pharmacology, very targeted.

A dosimetry change like this I think would be of concern in both situations, but of a major concern for a pleiotropic molecule.

I think one of the issues with respect to this technical assessment hierarchy, as I refer to it, is that in some point in time, you may conclude that, in aggregate, the differences are so concerning that you're actually looking that you're producing a different molecule.

If you conclude that that molecule, the

product attributes are likely to be very different, then I think you're talking about a fairly large development program, including all of the preclinical assessments and all of the clinical assessments that innovators do.

We're not debating the degree of CMC characterization. I think it's really the issues where the CMC characterization is supporting the conclusions on those first two bullets, that you're looking with something that is reasonably the same, and depending upon the data that is generated in the other three areas and the outcomes of that data and the conclusions derived thereof, really presents conceptually what some view as a minimum data set and what might be acceptable, essentially, for various regulatory authorities to consider acceptable for approval.

Some may conclude that you have to have all of those data sets represented in a registration dossier. I'm in that camp. I can't imagine a single assessment, and I may different with some of my colleagues at the agency, that they

would accept for approval a molecule that has no toxicologic assessment, for many of the reasons that we talked about here.

DR. OLESON: I just want to concur with Jim quite a bit on what he just said, but in this situation, I'm not sure I would do more tox work. I think you have a bigger problem.

I think, to what Jim was saying, I'm not totally convinced that the biochemical evaluation should be revisited in some other way.

The second thing is, someone alluded to it, I think Mary Ellen, the whole issue Mark Rogge brought up about tissue distribution changes. That would be the first thing to look at and evaluate in an animal model, not doing anymore tox work, going back and really evaluating the biochemical differences to make sure they are the same, and then, finally, if everything looks pretty good from that standpoint and the tissue distribution is similar still, even though the PK half-life is different clearance, then you might consider a single-dose human PK study to assess it in humans

to make sure the animal model is not telling you something felonious, but be very careful in terms of making the decision to move forward with the product development in this case.

DR. CAVAGNARO: Only DIA, Jessica Kumsa, can unlock this computer.

DR. EL-HAGE: I apologize. The technical problems continue.

We did, as a group, make up a couple summary slides. I apologize. We are having trouble getting these slides to come up.

Basically, we tried to summarize what we felt was a possible approach to the issue of toxicology studies, and I had two summary slides. One discusses product attributes that would be supportive of a minimal nonclinical safety evaluation, and that would be the circumstances when, according to biochemical characterization, potency characterization, that the follow-on protein was equivalent to the innovator product.

It was a low complexity protein. They had comparable PK profiles, either in nonclinical

studies and/or in clinical studies.

It had a well understood mechanism of action, extensive pharmaceutical knowledge and experience, multiple approved products, extensive clinical experience, multiple approved products, extensive clinical experience, and that it was a replacement therapy or a large therapeutic index compound.

I guess we still haven't clearly defined what we think that minimal data set might be, but many of us, in our private discussions, felt that it might be a well designed two-week, four-week tox study, with PK/PD, tox end points, comparative immunogenicity end points, and if Jim thinks of anything I forgot.

But one well designed study that you could do multiple cross-species comparison, and our preference would clearly and our recommendation would clearly be that that study included a comparator innovative protein.

The second case example would be product attributes, which would warrant nonclinical safety

evaluations on a case-by-case basis, when you might need more than this minimal data set, and that would be compounds with high molecular complexity, new process impurities, high heterogeneity, PK differences or changes in formulation, or changes in route of administration of the product, where the mechanism of action was poorly understood, where there is limited pharmaceutical experience, or when there is narrow therapeutic index.

So we felt any of those later characteristics, we'll make sure that these slides get on the DIA slide set for those of you who are interested in having a copy.

But that was a consensus opinion of people on the panel and we thought a way to move forward and perhaps a way to seek constructive comment from the audience.

DR. BLACK: Jeri, could I make a brief comment? This is Lauren Black, from Charles River Labs.

I would be interested in seeing, when we have a chance to see it, the qualifiers that you

put before the simplistic case as being the things that you would feel like probably would allow for a less restrictive package.

I think that one of the things that caught my attention in a lot of the discussions and comments is several people, and I agree, also, that these cases that we think we might be able to do with a little bit less, like do one well designed study and be done with it, really hinge--aren't really dependent at all upon complexity of the product.

It seems like all of the audience and I agree that the molecular complexity or the lack thereof, we don't feel comfortable enough agreeing that a physicochemical characterization that says that something is not complex really will predict the clinical efficacy or the clinical safety will be the same between an innovator and a generic.

We don't trust the biochemical characterization. Because of that, it necessitates that we go on to an empirical characterization that goes through pharmacokinetics and pharmacodynamics

and an examination of relevant models.

So I would be interested in seeing if you could remove molecular complexity or get other comments.

DR. EL-HAGE: I think there was some debate whether a low complexity protein, case examples being, perhaps from my division, an insulin or growth hormone, might be able to have no tox workup. I think most of us felt that that wouldn't be appropriate.

Those are the low complexity end of the molecular spectrum. That even for those, we would feel more comfortable in having this minimal data set that looks at multiple parameters to give us a confirmation of comparability.

Ideally, we would like to have that. I think there has been some debate about that in the past.

I think most people felt comfortable that if we had that minimal data set for these better understood, maybe it's not low complexity, maybe its' extensive pharmaceutical experience is the

key. You know, we have multiple products approved, with multiple means of manufacture, and we haven't had any adverse clinical experience with those products, and, therefore, our level of comfort is greater.

DR. FACKLER: If I could just ask a question. You mentioned human growth hormones. Which one would you choose as the comparator for the follow-on protein?

DR. EL-HAGE: I don't think we have made a statement. We have allowed sponsors to make that decision on their own. We haven't put forward a reference product or an innovator comparator.

DR. FACKLER: The same would be true, I think, for the interferons. I guess the question is for an abbreviated process, if interchangeability isn't what is desired, what is the value in the comparator? And, of course, again, I go to which comparator would you choose if you weren't--

DR. EL-HAGE: I think Theresa Reynolds made good point when she spoke. She said if

you're a follow-on company and you don't really have a good handle on what the tox profile of that innovator looks like, how do you make a comparison to know whether your compound is the same or different.

Most of us feel that the best way to say you're at least comparable in this limited data set is to do a head-to-head comparison with the innovator product.

DR. FACKLER: So would the agency then be ultimately deciding what the right comparator is for human growth hormone?

DR. EL-HAGE: I don't think it would be the subject of this guidance and I think that would be something that our legal people would have to read in on. I'd rather not comment.

DR. FACKLER: But if the guidance--

DR. EL-HAGE: I don't know if they've had this discussion in biologics about the interferons, but I know we have not specifically recommended--actually, we haven't even specifically stated that there was an absolute requirement for

the comparator.

We recommend that you use a comparator. I think most of us feel we will get the best data if the study includes a comparator, but we have not put forward that absolute requirement.

DR. WEIR: I think as far as which comparator would be best to use, some scientific justification, if there is one, to choose what would be the best comparator. But at least for products that I have dealt with, we have not had any products quite like the growth hormone. We've had multiples.

Certainly, for the interferons, we do see studies there where there will be a comparator, and those the company has picked their own, made their own choice as far as comparator goes.

DR. ANDREWS: Paul Andrews, ImClone. You mentioned two or four-week studies is probably the default, but I just want to ask you to consider--I know of numerous real life examples where you need three months and sometimes even six or nine months to elicit the toxicity of concern for a product,

and there will probably be cases when you need much longer term studies for comparative assessment.

DR. EL-HAGE: Those would probably fall into the more extensive data set case-by-case.

DR. ANDREWS: Exactly.

DR. EL-HAGE: And all of us here encourage you--we have a pre-IND process. If you don't want to have a pre-IND meeting and you have questions about your follow-on development plans, send in the questions.

I know our division and I know biologics has a routine policy of being very available for feedback. We are seeing inquiries about these products. We will be happy to give you our best advice, but you have to understand that the guidances are in development.

DR. GREEN: I think since growth hormone was mentioned, I think that is a good example to think about, because the focus of our panel here was the extent of toxicologic assessment.

Now, there are some issues specific to growth hormone, where it is active in a variety of

animal models, but, in fact, in one of the models, it is actually used as the bioassay, as a growth assay.

You could conceive, essentially, of a head-to-head comparison where that model essentially was used as the basis of your toxicologic assessment in a head-to-head comparison and combining, essentially, PK/PD toxicity end points, which are known, and, again, satisfying what might be viewed as a requirement of a full complement of data.

Now, in that case, it may be very different from another product, but, again, conceptually, this, I think, is what, when we talked about this, would be a requirement.

I cannot envision a situation, for all the reasons that we talked about, that that assessment would be not viewed as valid to support safe use conditions and the support of registration.

But that certainly is a different extent of study than many of the innovators did when they initially got growth hormone registered.

DR. EL-HAGE: Well, the computer continues to crash every time we try to open these slides.

I think our time is up for this session.

So you are free to leave. We can get together with our next group.

[Whereupon, the session concluded.]

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